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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,408	07/02/2003	Michele Boix	17571 (AP)	4873

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BRENT A. JOHNSON
ALLERGAN, INC.
T2-7H
2525 Dupont Drive
Irvine, CA 92612

EXAMINER	
SILVERMAN, ERIC E	
ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/614,408	BOIX ET AL.	
	Examiner	Art Unit	
	ERIC E. SILVERMAN	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-26,70-84 and 88-101* is/are pending in the application.

4a) Of the above claim(s) *22-26,95 and 97-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-85,88-94,96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-25-2008 has been entered.

Election/Restrictions

Newly submitted claims 95 and 97-101 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claim is directed to a process of making the product of claim 70. A product is distinct from a process when, *inter alia*, the product can be made by a materially different process. For example, the Montanari reference shows that when certain CLO microparticles are irradiated at room temperature, there is no additional aggregation, and so the product can also be made by irradiating at room temperature.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 95 and 97-101 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

It is noted that claims 96 purports to depend on claim 95, but recites a composition, not the method of claim 95. Claim 96 is therefore not withdrawn at this time, as the elected invention is a composition, but if this claim is amended to read on the withdrawn method of claim 95, then it should be withdrawn. Applicants' are reminded of their potential right of rejoinder, which was set out in detail in the office action mailed 4/30/2006.

Claims 22-26 70-85 and 88-101 are pending. Claims 22-26, 95, 97-101 are withdrawn. Claims 70-85, 88-94 and 96 are treated on the merits.

Claim Objections

Claim 96 is objected to because of the following informalities: this claim depends on withdrawn claim 95. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-85 and 88-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the examples in the specification, does not reasonably provide enablement for any other combination of drug/polymer microparticle. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Enablement is considered in view of the factors enumerated in MPEP 2164.04(a), which serve as a guide to determining whether the experimentation needed by the artisan to make and use the claimed invention is undue. All of these factors have been considered, and the most relevant are discussed in detail below.

- *The breadth of the claims*. Instant claims are drawn to irradiated polymeric materials made by irradiation at 5 C or less, so that the microparticles are less aggregated than if irradiation was performed at greater than 5 C. The microparticles comprise at least one particle and an active, but open ended comprising language means that they may also include other ingredients. The broadest claims do not limit the nature of the polymeric component or the active agent, while other claims specify that the polymer be PLGA. The broadest claims do not specify the nature of the active agent, while other claims require tazartene. No claim requires the combination of PLGA and tazartene, and no claim excludes other active or inactive components of any time.
- *The nature of the invention*. Irradiation with gamma rays is a common, art recognized effective means of sterilizing microspheres that are to be used for medicinal purposes. Applicants have recognized that some microspheres aggregate upon gamma ray irradiation at room temperatures, which is undesirable, especially because such aggregation alters the release properties of the drug from the polymer. Applicants have invented a way of preventing this aggregation in the particular

microsphere of the examples by irradiating the microspheres at low temperatures.

- *The level of predictability in the art*. Irradiation of PLA or PLGA microspheres with gamma rays yields unpredictable results, according to Montanari et al. at page 318, left column. Montanari shows several examples where similar microspheres are irradiated, but the results are contradictory. For example, whereas captopril release rates decrease upon irradiation, release rates of progesterone increase (the instant specification correlates aggregation with changes in release rate, so Montanari is understood to show that the changes in aggregation are unpredictable). Also, the nature of the drug being used is important. PLA degradation is described to be independent of methadone loading, but higher with increased loading of prometazine, and lower with incorporation of tetracycline. With regard to aggregation, Applicants have alleged that the microparticles of Rodgers and Tice (US 5,534,261 and 4,835,139, respectively) aggregate substantially after irradiation. However, the particles of Montanari, which are made of the same material as that of Rodgers and Tice, do not substantially aggregate upon irradiation, especially upon irradiation under vacuum (see Figure 2, which shows that the particle size distribution in Montanari does not change significantly after irradiation). Furthermore, the presence of a drug alters the effects of irradiation on aggregation. Figure 2 of

Montanari shows that without the drug CLO, irradiation causes an overall very small increase in particle size, which indicates some small amount of increased aggregation. However, when CLO is added, the particle size distribution shows a shift towards smaller particles, suggesting that in this case irradiation actually reduced aggregation of the particles (note that aggregation can be correlated to particle size changes because aggregated particles are larger than non-aggregated particles). Accordingly, the result of irradiation on PLA and PLGA particles is quite unpredictable.

- *The amount of direction provided by the inventor and the existence of working examples*. The working examples only show the effects of irradiation at room temperature and at an undisclosed temperature less than 5 C on one particular microparticle, which contains PLGA and tazarotene and is formed from a solvent evaporation technique. There is no useful information given on what other polymers and drugs combinations would also give the same results. To give an idea of how sparse the teachings of the specification are (outside of the examples, which are instructive but limited in scope) note that of the 14 page specification, 2 pages are background information, a full 4½ pages are merely a long list of drugs (without any comment that addresses how these drugs may interact with PLGA or any other polymeric microsphere), and 3 pages are devoted to the Examples. There is no

teaching, or even contemplation, of how to choose a polymer and drug combination that will give the claimed results (lack of aggregation after irradiation)

- *The amount of experimentation required by the artisan*. The artisan who wished to make any aspect of this invention outside of that in the examples would essentially be starting the inventive process from scratch. The artisan would have to choose an active agent and polymer, from essentially limitless possibilities, make microspheres from this combination (wherein the microspheres may or may not include additional active agents, more than one polymer, and other excipients), and then determine whether or not irradiation actually gives aggregated particles. Given that the art indicates that the results of combining a drug with PLGA is unpredictable, it is even more unpredictable when the polymer is not specified (as in most of the claims) and wherein the drug is also not specified (as in most of the claims). The artisan would have no idea, when starting to make the claimed invention, as to which combinations would actually give non-aggregated particles after irradiation at low temperatures.

Because the art is recognized to be unpredictable, and because the disclosure gives little guidance, the experimentation required by the artisan to make the claimed invention would be similar to that required by one just beginning the path towards making a new invention. Most importantly, the disclosure does not show that irradiation

at less than 5 C eliminates or reduces the unpredictability in the art. At best, the disclosure points the artisan (metaphorically) to a forest without any markings on the trees that might indicate how to pass through. The claims are therefore not fully enabled by the disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 96 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 96 recites the limitation "therapeutic composition" in claim 95. There is insufficient antecedent basis for this limitation in the claim. Claim 95 is drawn to a method of making such compositions, not to the composition itself.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 70-72, 27-79, 81-83, 88-93, and 96 are rejected under 35 U.S.C. 102(b) as being anticipiated by Montanari.

Montanari teaches gamma irradiated PLGA microparticles with the drug CLO. The particle diameters are within the range of instant claims. Although the particles are not said to be irradiated at 5 C or less, in instances when they are irradiated under vacuum, the aggregation actually decreases as compared to the particles before irradiation or as compared to the particles when irradiated in air, as reflected by the

decrease in particle sizes in Figure 2 B for CLO irradiated under vacuum. The particles are also lyophilized (section 2.1). Thus, although prepared by a different method, the microparticles of Montanari are materially identical to those of instant product by process claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 72, 80, 84 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Montanari in view of Us 6,365,632 to Perricone and US 5,534,261 to Rogers.

What is lacking in Montanari is tazaotene.

Perricone teaches tazarotene as a useful retinoid active. Rodgers shows that retinoids can be used in gamma irradiated microparticles.

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use tazarotene in the particles of Montanari. The motivation would be to obtain the art-recognized therapeutic benefits of this agent. Because Rodgers teaches that retinoids are useful when formulated in PLGA microparticles, the artisan would enjoy a reasonable expectation of success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC E. SILVERMAN whose telephone number is (571)272-5549. The examiner can normally be reached on Monday to Thursday 7:00 am to 5:00 pm and Friday 7:00 am to noon.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571 272 0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric E Silverman/
Examiner, Art Unit 1618